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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/448,633	11/24/99	WEI	A 53091USA8B

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MORAN, M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev.11/00)

1- File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/448,633	WEI ET AL.	
	Examiner	Art Unit	
	Morjorie Moran	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☒ Other: *detailed action* .

Election/Restrictions

In response to arguments set forth in the response filed 4/9/01, claims 1-21 are hereby rejoined. An action on the merits of pending claims 1-21 follows.

Claim Rejections - 35 USC § 112

Examiner's note: the term "including" recited in the claims is interpreted to be open claim language, equivalent to --comprising--.

It is noted that the term "TEXAS RED", recited in claims 8 and 18, is a tradename. However, as the compound referred to under that name is available from several sources and is commonly used in the art to refer to a particular structure, use of the name does not render the claims indefinite. Although X-Rhodamine and Rhodamine B are capitalized in the claims, these names do not appear to be trade names. Again, the compounds referred to by these names are available from several sources and each term is commonly known in the art to refer to a particular structure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "sufficiently" in claims 1, 12 and 21 is a relative term which renders the claims indefinite. The term "sufficiently" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what degree of proximity is "sufficiently" close, therefore the claims are indefinite.

The term "essentially" in claims 1, 12, and 21 is a relative term which renders the claims indefinite. The term "essentially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 1 recites a "method of biological assay" in line 1, then recites steps of providing an enzyme substrate and cleaving the substrate. An "assay" implies measurement or detection of something, such as a compound, a characteristic (e.g. activity) of a compound, etc. It is unclear what the biological assay is intended to be used for (e.g. detection only, measurement and detection, inhibition, binding, etc.), and it is unclear what is being "assayed" (an enzyme, a substrate, an inhibitor, ability to fluoresce, binding affinity, etc.) therefore claim 1 is indefinite.

Claims 21 recites a method of detecting a microorganism in line 1, then recites steps of providing an enzyme substrate and cleavage of a bond to produce an increase of fluorescence intensity. Claim 21 does not recite a correlation between either bond cleavage or fluorescence intensity increase and detection of a microorganism. In the absence of a correlating step, it is unclear if a microorganism is actually detected in the method, therefore the claim is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-4, 6-8, 10, 12-13, and 15-18 are rejected under 35 U.S.C. 102(b) as being anticipated by GARMAN *et al.* (GB 2278356) with support from ROHATGI *et al.* (J. Phys. Chem.

(6/1966) vol. 70 (6), pages 1695-1701) and WEI *et al.* (Anal. Chem. (5/1994), vol. 66 (9), pages 1500-1506).

GARMAN teaches a protease substrate (p. 13) and assay method using the substrate wherein the substrate is cleaved by an enzyme and an increase in fluorescence is observed (pp. 14-15), wherein the substrate comprises a flexible peptide and two fluorescence groups which are fluorescein and tetramethylrhodamine (substrate D on pages 13-14). ROHATGI provides support that both fluorescein and tetramethylrhodamine are capable of dye-stacking (p. 1696 and 1699) and WEI provides support that fluorescein and tetramethylrhodamine attached to a peptide can interact to "essentially" self-quench the fluorescence groups (p. 1503, Figure 3A), therefore claims 1, 3, 6-8, 12, 15-18 are anticipated. GARMAN's substrate comprises Peptide II (p. 13), which is 14 amino acids in length. GARMAN teaches that each amino acid is 3.8 Å, therefore a peptide of 14 amino acids is about 53.2 Å, therefore if the C-terminus and N-terminus are labeled with the dye groups (i.e. the furthest distance possible), the dye groups will be separated by at most 53.2 Å, therefore claims 4 and 13 are anticipated. WEI also provides support that distances of 47-54 Å allow up to 70% quenching of fluorescence (pp. 1503-1504). Staphylococcal V8 protease is an aspartic protease, therefore claim 10 is anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 and 10-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over GARMAN *et al.* (GB 2278356) as supported by ROHATGI *et al.* (J. Phys. Chem. (6/1966) vol. 70 (6), pages 1695-1701) and WEI *et al.* (Anal. Chem. (5/1994), vol. 66 (9), pages 1500-1506), and in view of KOMORIYA et al. (US 5,714,342).

Claim 12 recites a protease substrate comprising two fluorescence dye groups bound to a flexible peptide wherein the dye groups are close enough to self-quench through intramolecular dimerization or dye-stacking. Claim 1 recites a biological assay method comprising providing an enzyme substrate similar to that of claim 12 wherein the substrate is further limited to comprise two or more dye groups and one or more enzymatically cleavable bonds; and the method also comprises a step of cleaving the one or more cleavable bonds to thereby produce an increase in fluorescence intensity. Claims 1 and 14 further limit the dye groups to be identical. Claims 3 and 15 further limit he dye groups to comprise a fluorescence donor and acceptor. Claims 4 and 13 limit the distance between the dye groups to be less than 100 Å. Claims 6 and 16 further limit the dye groups to be planar. Claims 7-8 and 17-18 further limit the dye groups to be fluorescein, rhodamine, cyanine, tetramethylrhodamine, X-Rhodamine, Rhodamine B, or TEXAS RED. Claim 10 further limits the method to one wherein enzymatic cleavage is performed by an aspartic, metallo-thio, serine, retroviral, or trypsin

protease. Claim 11 further limits the method to one wherein fluorescence intensity is increased at least 10-fold compared to an intensity increase in conventional assay kits comprising a protease substrate.

GARMAN, as supported by ROHATGI and WEI, teaches a protease substrate and biological assay method, as set forth above. WEI also provides support that singly labeled substrates (i.e. those previously known in the art) do not exhibit fluorescence quenching whereas fluorescence of a substrate labeled with two fluorescent dyes is 90% or 98% quenched compared to the singly labeled substrates. A substrate comprising only a single fluorescent dye would therefore not be expected to exhibit an increase in fluorescent intensity upon cleavage. GARMAN teaches that his doubly labeled substrate exhibits a 7-8-fold increase in intensity upon cleavage (Figure 2). As the singly labeled substrates would not be expected to show any increase in intensity upon cleavage, GARMAN's Figure 2 indicates a 7-8-fold increase over "conventional" substrates such as would be found in "conventional assay kits". GARMAN, as supported by ROHATGI and WEI, does not teach "at least" a 10-fold increase in fluorescence intensity in his method compared to "conventional assay kits" using a protease substrate; nor does GARMAN, as supported by ROHATGI and WEI teach a substrate wherein the dye groups are identical.

KOMORIYA teaches a protease substrate comprising an enzyme cleavage site and two fluorescent dyes, wherein said dyes undergo quenching due to dye stacking, or dimerization (col. 9, lines 5, 25-26 and col. 31, line 45-col. 33, line 15). He also teaches a variety of enzymes for use with said substrate (col. 12-15, Table 2), donor and acceptor fluorophores of planar configuration, preferably tetramethylrhodamines and rhodamine X acetamide (col. 15, line 43-col. 16, line 37). KOMORIYA also teaches that use of a double fluorophore substrate shows a dramatic increase in fluorescent intensity compared to the same method using another

substrate (col. 30, lines 53-56), and teaches that substrates may be doubly-labeled with the same fluorophore (col. 31, line 49-col. 33, line 15), and teaches that an advantage for use of a homo-doubly-labeled substrate is that a homo-labeled substrate requires use of only a cutoff filter whereas the hetero-labeled substrates require use of an interference filter in methods of detection (col. 34, lines 16-27).

It would have been obvious to one of ordinary skill in the art at the time of invention to have labeled the substrate (Peptide II) of GARMAN, as supported by ROHATGI and WEI with the rhodamine combination taught by KOMORIYA to result in the "at least" 10-fold increase in fluorescence where the motivation would have been to use a combination of dyes known to result in high fluorescence intensity in order to optimize, or increase sensitivity, of the method. It would also have been obvious to one of ordinary skill in the art at the time of invention to have doubly labeled the substrate of GARMAN, as supported by ROHATGI and WEI with any of the fluorophores taught by KOMORIYA to be satisfactory for homo-double-labeling of a protease substrate (e.g. any of those shown in Table 9 except fluorescein) where the motivation would have been to facilitate use of the substrate in methods of detection, as suggested by KOMORIYA's teaching that homo-double-labeled substrates supply an advantage in methods of detecting enzymes, as set forth above.

Claims 9 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over GARMAN *et al.* (GB 2278356) as supported by ROHATGI *et al.* (J. Phys. Chem. (6/1966) vol. 70 (6), pages 1695-1701) and WEI *et al.* (Anal. Chem. (5/1994), vol. 66 (9), pages 1500-1506), in view of KOMORIYA *et al.* (US 5,714,342), as applied to claims 1-8 and 10-18 above, and further in view of HEATH, JR. *et al.* (US 5,235,039).

Applicant claims a protease substrate and biological assay using the substrate, as set forth above. Claims 9 and 19 further limit the substrate to one comprising 2-10 amino acids wherein the dye groups form a stack and the substrate comprises at least one enzyme-specific cleavable bond.

GARMAN, ROHATGI , WEI, and KOMORIYA teach and make obvious a flexible protease substrate labeled with two fluorescent dye groups which dimerize or stack so as to self-quench, wherein the substrate comprises at least one enzyme cleavable bond as set forth above. GARMAN, ROHATGI , WEI, and KOMORIYA do not teach a substrate comprising 2-10 amino acids.

HEATH, JR. teaches an octapeptide substrate for collagenase which is fluorescently labeled (col. 10, lines 23-34).

It would have been obvious to one of ordinary skill in the art at the time of invention to have substituted the octapeptide of HEATH for Peptide II in the substrate and method of GARMAN, ROHATGI , WEI, and KOMORIYA where the motivation would have been to measure vertebrate collagenase, as taught by HEATH (col. 10, lines 35-51).

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over GARMAN *et al.* (GB 2278356) as supported by ROHATGI *et al.* (J. Phys. Chem. (6/1966) vol. 70 (6), pages 1695-1701) and WEI *et al.* (Anal. Chem. (5/1994), vol. 66 (9), pages 1500-1506), and in view of MANAFI *et al.* (Microbiol. Reviews (9/1991), vol. 55 (3), pages 335-348).

Claim 21 recites a method of detecting a microorganism using the same steps as recited in claim 1.

GARMAN, as supported by ROHATGI and WEI teaches a biological assay wherein activity of a Staphylococcal aspartic protease is detected, as set forth above. GARMAN does not specifically teach detection of a microorganism.

MANAFI teaches that microbial cells can be detected by detecting a change in fluorescent intensity due to cleavage of a fluorogenic substrate (p. 336). MANAFI specifically teaches that fluorescent substrates can be used to detect Staphylococcus (p. 338).

It would have been obvious to one of ordinary skill in the art at the time of invention to have detected Staphylococcus using the substrate and method of GARMAN where the motivation would have been to use cleavage of a specific fluorescent substrate to detect and differentiate Staphylococcus, as suggested by MANAFI's teaching that specific Staph. species can be detected with a fluorescent substrate.

Allowable Subject Matter

Claim 20 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The following is a statement of reasons for the indication of allowable subject matter: The prior art does not teach the structure recited in claim 20. The prior art does not teach any motivation to pick the particular amino acid sequence recited in claim 20 as the peptide portion of the claimed substrate, nor does the prior art teach the claimed sequence as part of any other (e.g. larger) protease substrate, therefore claim 20 is not suggested by the prior art.

Drawings

The drawings are approved by the draftsperson.

Conclusion

Claims 1-21 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (703) 305-2363. The examiner can normally be reached on Monday to Friday, 7:30 am to 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (703) 308-4028. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to a Patent Analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Marjorie A. Moran
June 8, 2001

Marianne P. Allen
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